

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 November 2004 (18.11.2004)

PCT

(10) International Publication Number
WO 2004/099199 A1

(51) International Patent Classification⁷: **C07D 413/14**,
A61K 31/422, A61P 31/04

(21) International Application Number:
PCT/IB2003/001754

(22) International Filing Date: 6 May 2003 (06.05.2003)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

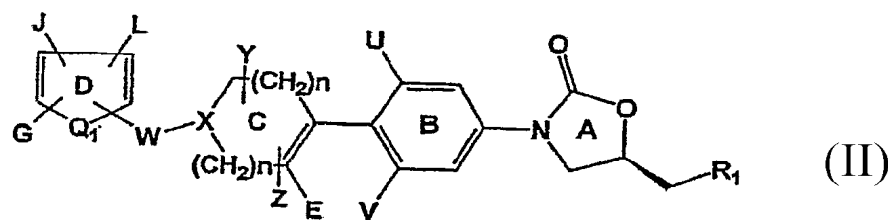
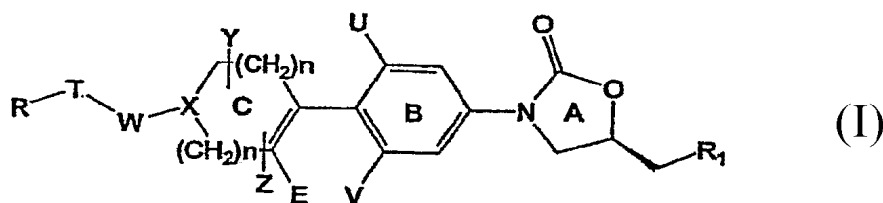
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OXAZOLIDINONE DERIVATIVES AS ANTIMICROBIALS



(57) Abstract: The present invention relates to certain substituted phenyl oxazolidinones of formula (I) or (II) and to the processes for the synthesis of the same. This invention also relates to pharmaceutical compositions containing the compounds of the present invention as antimicrobials. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacterioides* spp. and *Clostridia* spp. species, and acid fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium* spp.



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OXAZOLIDINONE DERIVATIVES AS ANTIMICROBIALS

FIELD OF THE INVENTION

The present invention relates to certain substituted phenyl oxazolidinones and to the processes for the synthesis of the same. This invention also relates to pharmaceutical compositions containing the compounds of the present invention as antimicrobials. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacterioides* spp. and *Clostridia* spp. species, and acid fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium* spp.

BACKGROUND OF THE INVENTION

Increasing antibacterial resistance in Gram positive bacteria has presented a formidable treatment problem. The enterococci, although traditionally non virulent pathogens, have been shown, when associated with Vancomycin resistance, to have an attributable mortality of approximately 40%. *Staphylococcus aureus*, the traditional pathogen of post operative wounds, has been resistant to Penicillin due to production of penicillinases. This resistance was overcome by the development of various penicillinase stable β lactams. But the pathogen responded by synthesizing a modified target penicillin binding protein- 2' leading to less affinity for β lactam antibiotics and a phenotype known as Methicillin Resistant *S. aureus* (MRSA). These strains, till recently were susceptible to Vancomycin, which inspite of its various drawbacks, has become the drug of choice for MRSA infections. *Streptococcus pneumoniae* is a major pathogen causing pneumonia, sinusitis and meningitis. Until very recently it was highly susceptible to penicillin. Recently though, different PBP 2' strains with different susceptibility to penicillin have been reported from across the globe.

Oxazolidinones are a new class of synthetic antimicrobial agents which kill gram positive pathogens by inhibiting a very early stage of protein synthesis. Oxazolidinones inhibit the formation of ribosomal initiation complex involving 30S and 50S ribosomes leading to prevention of initiation complex formation. Due to their novel mechanism of

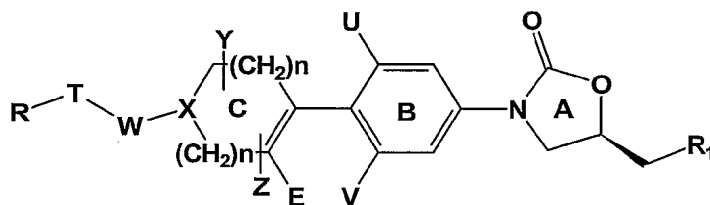
action, these compounds are active against pathogens resistant to other clinically useful antibiotics.

SUMMARY OF THE INVENTION

The invention involves the synthesis; identification and profiling of oxazolidinone molecules which have good activity against multiply resistant gram positive pathogens like MRSA, VRE and PRSP. Some of these molecules have activity against MDR-TB and MAI strains, while others have significant activity against important anaerobic bacteria.

The present invention provides processes for the syntheses of phenyloxazolidinone derivatives which can exhibit significant antibacterial activity against multiply resistant gram positive pathogens like MRSA, VRE and PRSP against MDR-TB and MAI strains, in order to provide safe and effective treatment of bacterial infections.

In accordance with one aspect of the invention, there are provided compounds having the structure of Formula I



FORMULA I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites,

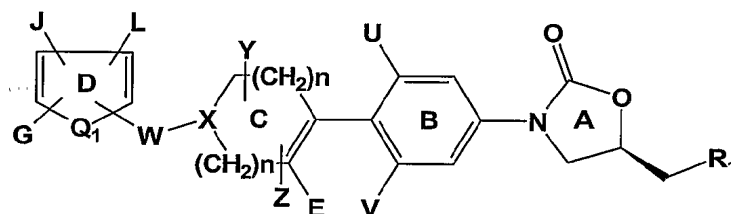
wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker **W**, for example, particular forms of **T** are selected from aryl and five membered heteroaryl which are further substituted by a group represented by **R**, wherein **R** is H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅, N(R₆, R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆, R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH=N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I, OR₄, SR₄, wherein R₄ is

- hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxy carbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH; R₅ is H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br and I, OR₅, SR₄, N(R₆, R₇); R₁₀ = H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl;
- n is an integer in the range from 0 to 3;
- X** is CH, CH-S, CH-O, N or CHNR₁₁, wherein R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkyl carbonyl, C₁₋₆ alkyl carboxy, aryl or heteroaryl;
- E** is hydrogen, hydroxy or lower alkyl (C₁₋₄);
- Y** and **Z** are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl or a C₀₋₃ bridging group;
- U** and **V** are independently hydrogen, optionally substituted C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I;
- W** is (CH₂)_{0-n'}, CO, CH₂NH, -NHCH₂, -CH₂NHCH₂, -CH₂N(R₁₁)CH₂-, CH₂N(R₁₁), CH(R₁₁), S, CH₂(CO), NH, O, NR₁₁, (CO)CH₂, N(R₁₁)CON(R₁₁), N(R₁₁)C(=S)N(R₁₁), SO₂, SO, wherein n' is an integer in the range from 0 to 3; R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkyl carbonyl, C₁₋₆ alkyl carboxy, aryl or heteroaryl; and
- R₁** is -NHC(=O)R₂, N(R₃, R₄), OR₃, -NR₂C(=S)R₃, -NR₂C(=S)SR₃, wherein R₂ is hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I, OH; R₃, R₄ are independently hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxy carbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH.

Particular compounds of Formula I have R_1 as acetamide, halogen, ether linked heteroaryl or amino-heteroaryl, substituted acetamide and the most preferred compounds in this series would be prepared as the optically pure enantiomers having the (S)-configuration according to the Cahn-Ingold-Prelog notation at C_5 of the oxazolidinone ring.

Other particular compounds of Formula I containing D ring as furanyl, thienyl, and pyrrolyl ring systems and further substituted by substitutions G, J and L are represented by Formula II



Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2 , R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxy carbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, R_1 can be of the formula $-NH(C=O)R_2$ wherein R_2 is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2Cl , $CHCl_2$, CCl_3 ; and R_3 , R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

U and V are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and Z are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1 - C_4);

W is $(\text{CH}_2)_{0-n'}$, C=O, CH_2NH , NHCH_2 , CH_2NHCH_2 , $\text{CH}_2\text{N}(\text{R}_{11})\text{CH}_2$, $\text{CH}_2\text{N}(\text{R}_{11})$, $\text{CH}(\text{R}_{11})$, S, $\text{CH}_2(\text{C}=\text{O})$, NH, O, $(\text{CO})\text{CH}_2$, $\text{N}(\text{R}_{11})\text{CON}(\text{R}_{11})$, SO_2 , SO, NR_{11} , $\text{N}(\text{R}_{11})\text{C}(=\text{S})\text{N}(\text{R}_{11})$, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

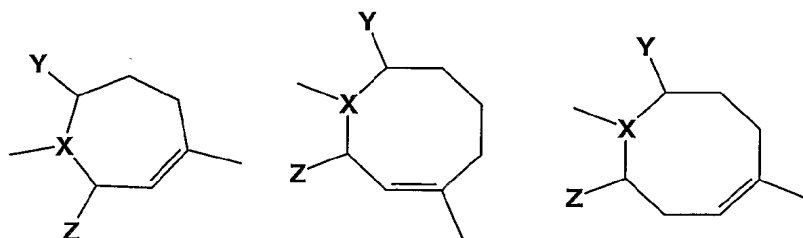
Q_1 is O, S or NR_{11} , wherein R_{11} is as defined above;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, $-\text{CN}$, COR_5 , COOR_5 , $\text{N}(\text{R}_6, \text{R}_7)$, $\text{NHCOC}(\text{R}_8, \text{R}_9, \text{R}_{10})$, $\text{CON}(\text{R}_6, \text{R}_7)$, CH_2NO_2 , NO_2 , CH_2R_8 , CHR_9 , $-\text{CH}=\text{N}-\text{OR}_{10}$, $-\text{C}=\text{CH}-\text{R}_5$, OR_5 , SR_5 , $-\text{C}(\text{R}_9)=\text{C}(\text{R}_9)\text{NO}_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4 , SR_4 , wherein R_4 is as defined above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5 , SR_4 , $\text{N}(\text{R}_6, \text{R}_7)$; $\text{R}_{10}=\text{H}$, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

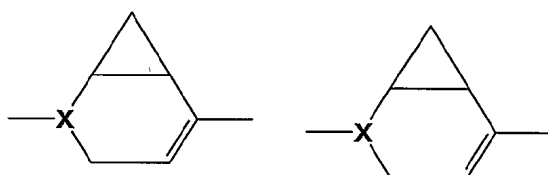
n is an integer in the range from 0 to 3.

In some compounds represented by Formula II, ring C may be 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, for example:

5

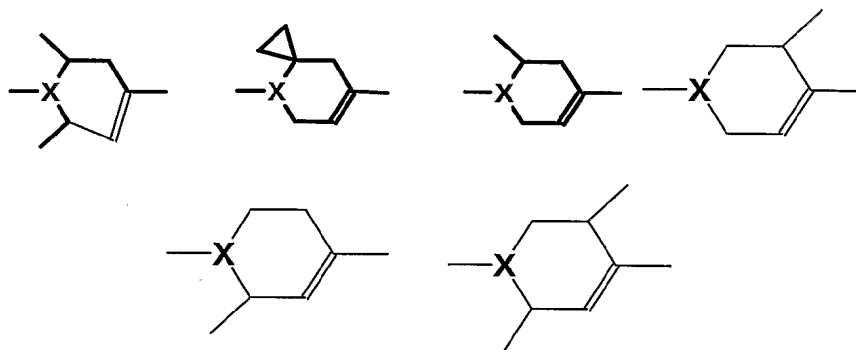


The ring C may be bridged to form a bicyclic system as shown below:



10

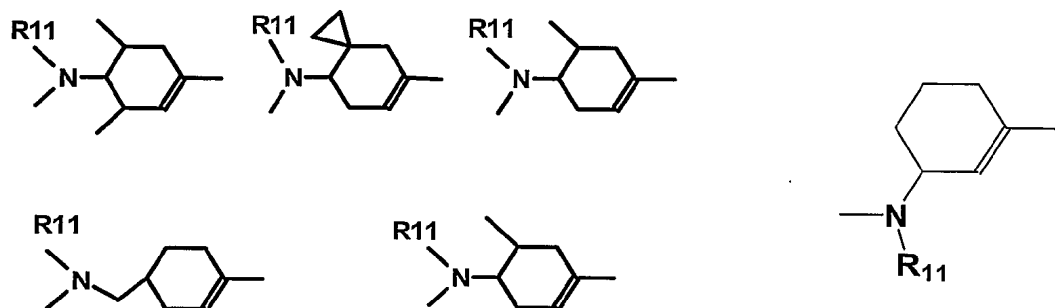
When ring C is optionally substituted at positions Y and Z, particular examples with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups are as shown below:



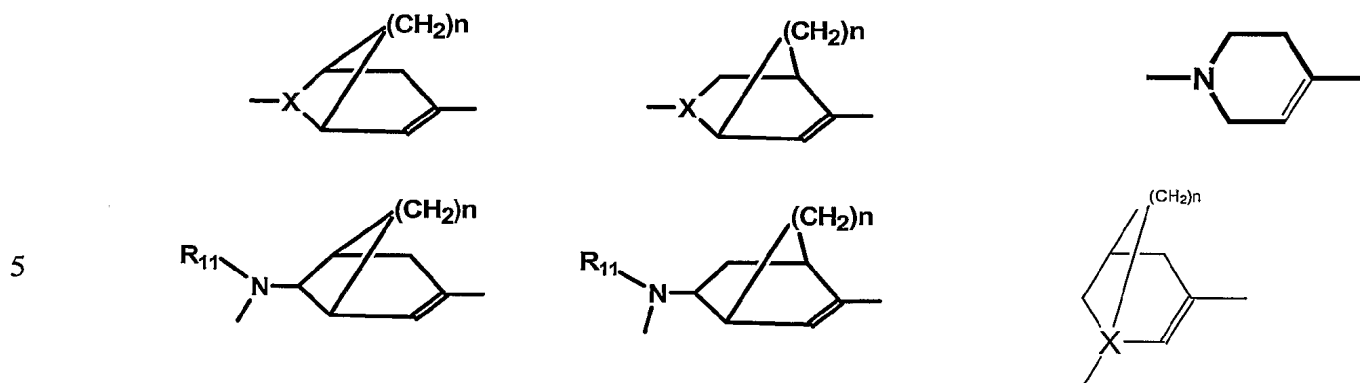
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When ring C is 6-membered in size and X is $-\text{CH}(\text{NHR})$, or $-\text{CHCH}_2\text{NHR}-$, the following rings are preferred ones wherein R_{11} is as defined earlier.

20

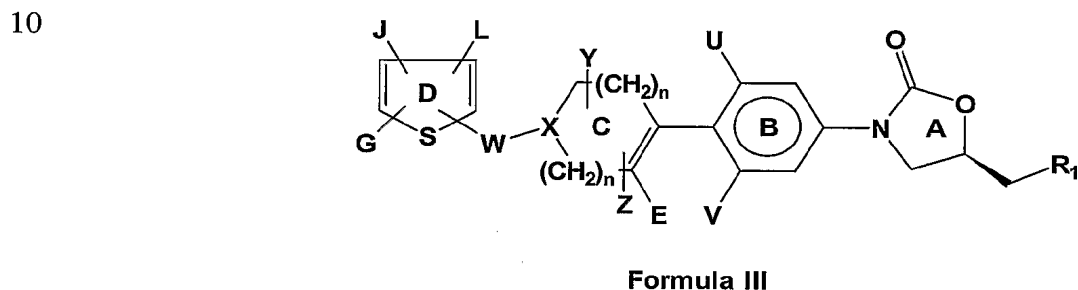


In addition to the above, ring C also includes the following structures:



Wherein n is as defined earlier.

In accordance with a third aspect of the present invention, there are provided compounds represented by Formula III



wherein

15 **R₁** is --NHC(=O)R_2 , $\text{--N(R}_3\text{,R}_4\text{)}$, $\text{--NR}_2\text{C(=S)R}_3$, $\text{--NR}_2\text{C(=S)SR}_3$ or --OR_3 wherein **R₂**, **R₃**, **R₄** are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, **R₁** can be of the formula --NH(C=O)R_2 wherein **R₂** is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2Cl , CHCl_2 , CCl_3 ; and **R₃**, **R₄** can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

20

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, or a C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or CHNR₁₁, wherein R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl carbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C₁₋₄);

5 **W** is (CH₂)_{0-n'}, C=O, CH₂NH, NHCH₂, CH₂NHCH₂, CH₂N(R₁₁)CH₂, CH₂N(R₁₁), CH(R₁₁), S, CH₂(C=O), NH, O, (CO)CH₂, N(R₁₁)CON(R₁₁), SO₂, SO, NR₁₁, N(R₁₁)C(=S)N(R₁₁); wherein n' is an integer in the range from 0 to 3; R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl carbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl;

10 **G, J, L** are independently H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅, N(R₆, R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆, R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH = N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I, OR₄, SR₄, wherein R₄ is the same as above; R₅ is H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently selected from H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I, OR₅, SR₄, N(R₆, R₇); R₁₀ = H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and
15 n is an integer in the range from 0 to 3.

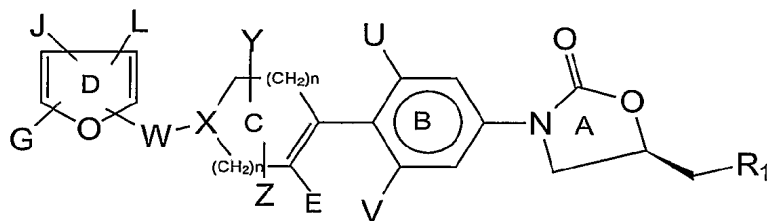
20 Particular G, J and L substitutions can include nitro, aldehydes and halides.

Other particular compounds of Formula III are as follows:

Compound No 2: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl (5-nitro) methyl}] 1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

25 Compound No 3: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide.

In accordance with a fourth aspect of the present invention, there are provided compounds represented by Formula IV



Formula IV

5 wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, $-OR_3$ wherein R_2 , R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxy carbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; for example, R_1 can be of the formula $-NH(C=O)R_2$ wherein R_2 is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2Cl , $CHCl_2$, CCl_3 ; and R_3 , R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

U and V are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and Z are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

15 X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

20 W is $(CH_2)_{0-n'}$, $C=O$, CH_2NH , $NHCH_2$, CH_2NHCH_2 , $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2 , SO, NR_{11} , $N(R_{11})C(=S)N(R_{11})$, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

Q_1 is O, S or NR_{11} , wherein R_{11} is as defined earlier;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, $-CN$, COR_5 , $COOR_5$, $N(R_6, R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2 , NO_2 , CH_2R_8 , CHR_9 , $-CH=N-OR_{10}$, $-C=CH-R_5$, OR_5 , SR_5 , $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4 , SR_4 , wherein R_4 is as above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5 , SR_4 , $N(R_6, R_7)$; R_{10} = H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3.

Particular G, J and L substitutions are nitro, aldehydes and halides.

A particular compound of Formula IV is

Compound No. 5: 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one.

Compounds of the present invention can be useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic Gram-positive bacteria, including multiply-antibiotic resistant staphylococci and streptococci as well as anaerobic organisms such as *Mycobacterium tuberculosis* and other mycobacterium species.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, suppositories and ointments. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders or tablets disintegrating agents; it can also be as finely divided solid which is in admixture with the finely divided active compound. For the preparation of tablets, the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets

preferably contain from about 5 to about 70 percent of the active ingredient. Suitable solid carriers are lactose, pectin, dextrin, starch, gelatin, tragacanth, low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Such solutions are prepared so as to be acceptable to biological systems (isotonicity, pH, etc.). Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents as desired. Aqueous suspension suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e. natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose and other well-known suspending agents.

Ointment preparations contain heavy metal salts of a compound of Formula I with a physiologically acceptable carrier. The carrier is desirably a conventional water-dispersible hydrophilic or oil-in-water carrier, particularly a conventional semi-soft or cream-like water-dispersible or water soluble, oil-in-water emulsion infected surface with a minimum of discomfort. Suitable compositions may be prepared by merely incorporating or homogeneously admixing finely divided compounds with the hydrophilic carrier or base or ointment.

The pharmaceutical preparations can be in unit dosage form. In such forms, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete capsules, powders in vials or ampoules, and ointments capsule, cachet, tablet, gel, or cream itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from less than 1 mg to several grams according to the particular application and the potency of the active ingredient.

5 In therapeutic use as agents for treating bacterial infections, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 3 mg to about 40 mg per kilogram daily. The dosages, however, may be varied depending upon the requirements of the patient and the compound being employed. Determination of the proper dosage for a particular situation is within the smaller dosages which are less than the optimum dose. Small increments until the optimum effect under
10 the daily dosage may be divided and administered in portions during the day if desired.

In one aspect, the invention provides process for the syntheses of compounds of Formulae I, II, III and IV. Pharmaceutically acceptable non-toxic acid addition salts of the compounds of the present invention of Formulae I, II, III and IV may be formed with inorganic or organic acids, by methods well known in the art.

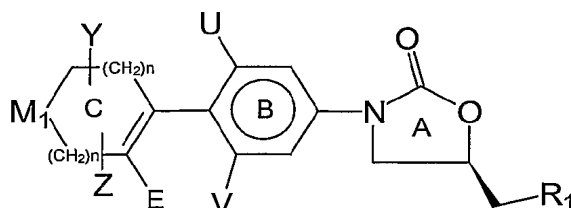
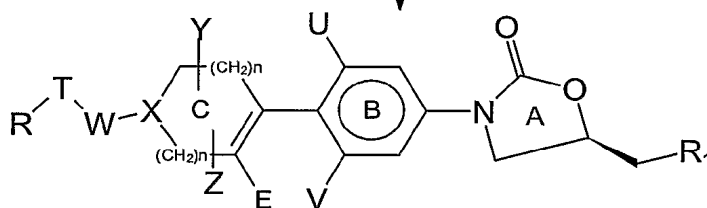
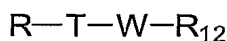
15 The present invention also includes within its scope prodrugs of the compounds of Formulae I, II, III and IV. In general, such prodrugs will be functional derivatives of these compounds which readily get converted *in vivo* into defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan of ordinary skill in the art.

20 The invention also includes pharmaceutically acceptable salts, the enantiomers, diastereomers, N-oxides, metabolites in combination with pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description, or may be learned by the
25 practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared by following the reaction sequences as depicted in the schemes defined below.

SCHEME-I**Formula V****FORMULA-I**

15 In scheme I, the amine of Formula V wherein M₁ is NH, NHR₁₃, -CH₂NHR₁₃, wherein R₁₃ is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy;

R₁ is -NHC(=O)R₂, -N(R₃, R₄), -NR₂C(=S)R₃, -NR₂C(=S)SR₃ or -OR₃, wherein R₂, R₃, R₄ are independently hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxy carbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH; for example, R₁ can be of the formula -NH(C=O)R₂ wherein R₂ is CH₃, CH₂F, CHF₂, CF₃, CH₂Cl, CHCl₂, CCl₃; and R₃, R₄ can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

20

E is hydrogen, hydroxy or lower alkyl (C₁-C₄);

Y and Z are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl or C₀₋₃ bridging groups;

U and V are independently hydrogen, optionally substituted C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I,

is reacted with a heteroaromatic compound of Formula R-T-W-R₁₂ wherein

5 T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring C with a linker W, for example, particular forms of T are selected from aryl and five membered heteroaryl which are further substituted by a group represented by R, wherein R is H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅, N(R₆,R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆, R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH=N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with one or more F, Cl, Br, I, OR₄, SR₄, wherein R₄ is hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxycarbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH; R₅ is H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently selected from H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br and I, OR₅, SR₄, N(R₆,R₇); R₁₀= H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl;

W is (CH₂)_{0-n'}, C=O, CH₂NH, NHCH₂, CH₂NHCH₂, CH₂N(R₁₁)CH₂, CH₂N(R₁₁), CH(R₁₁), S, CH₂(C=O), NH, O, (CO)CH₂, N(R₁₁)CON(R₁₁), SO₂, SO, NR₁₁, N(R₁₁)C(=S)N(R₁₁), wherein n' is an integer in the range from 0 to 3; R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl carbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl; and

R₁₂ is a suitable leaving group well known to one of ordinary skill in the art such as fluoro, chloro, bromo, SCH₃, -SO₂CH₃, -SO₂CF₃, Tos, OC₆H₅, -COOH or -CHO-.

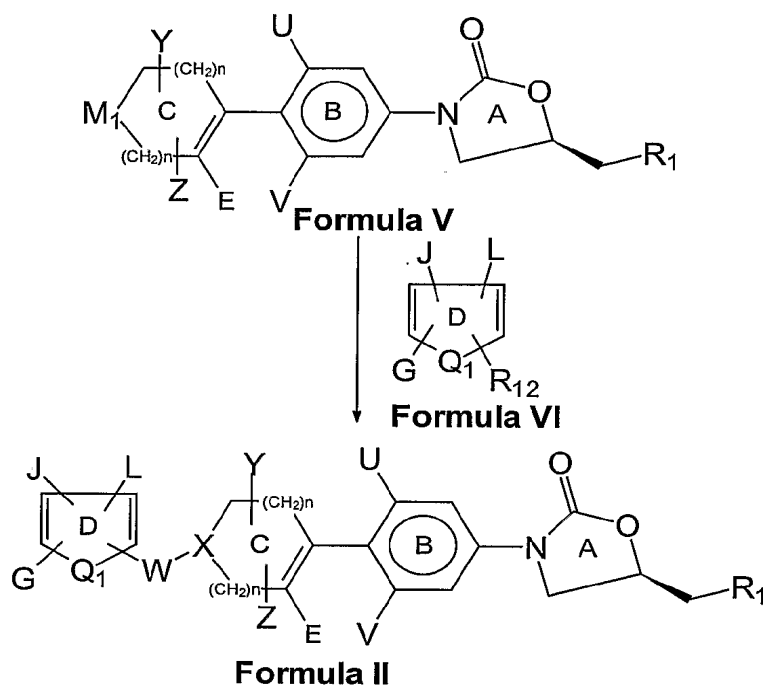
25 For the preparation of compounds of Formula I when W is equal to CH₂, the corresponding aldehyde can be used through a process of reductive amination and is attached to the amine of Formula V.

Similarly, for the preparation of compound of Formula I wherein W is equal to C = O, the corresponding acid can be used and the amine of Formula V can be acylated

through activated esters in the presence of condensing agents, for example, 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). Other methods of acylation can also be employed.

The preparation of the compound of Formula II can be accomplished as exemplified below by two methods A and B as shown in Scheme II:

SCHEME-II



Method A:

The amine of Formula V wherein M_1 is NH , NHR_{13} , $-CH_2NHR_{13}$, wherein R_{13} is H , ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy;

R_1 is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2 , R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxy carbonyl or C_{1-6} alkyl substituted with one or more of F , Cl , Br , I or OH ; for example, R_1 can be of the formula $-NH(C=O)R_2$ wherein R_2 is CH_3 , CH_2F , CHF_2 , CF_3 , CH_2Cl , $CHCl_2$, CCl_3 ; and R_3 , R_4 can be heteroaryl rings such as isoxazolyl, thiazolyl, or pyridyl;

E is hydrogen, hydroxy or lower alkyl (C_1 - C_4);

Y and **Z** are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl or C₀₋₃ bridging groups;

U and **V** are independently hydrogen, optionally substituted C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I,

is reacted with a heteroaromatic compound of Formula VI wherein

- 5 **R**₁₂ is a suitable leaving group such as fluoro, chloro, bromo, SCH₃, -SO₂CH₃, -SO₂CF₃, Tos, OC₆H₅, -COOH or -CHO-, other suitable leaving groups are well known to one of ordinary skill in the art;

Q₁ is O, S or NR₁₁, wherein R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl carbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl;

- 10 **G**, **J**, **L** are independently H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅, N(R₆, R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆, R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH=N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br and I, OR₄, SR₄, wherein R₄ is as defined above; R₅ is H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or
 15 heteroaryl; R₆ and R₇ are independently H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I, OR₅, SR₄, N(R₆, R₇); R₁₀=H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and
 n is an integer in the range from 0 to 3.

- 20 The reaction can be carried out in a suitable solvent, for example, dimethylformamide, dimethylacetamide, ethanol or ethylene glycol at a suitable temperature in the range of about -70°C to about 180°C to afford compounds of Formula II. The presence of a suitable base such as triethylamine, diisopropylamine, potassium carbonate, sodium bicarbonate is useful in some cases to improve the yield of the reaction.

- 25 The reductive alkylation of the amine intermediate of Formula V with the corresponding heterocyclic aldehydes of the Formula VI, such as furaldehyde (Q₁ = O, R₁₂ is CHO) using reducing agents well known to one of ordinary skill in the art such as sodium triacetoxyborohydride or sodium cyanoborohydride gives the products of Formula II, wherein W=CH₂ as shown in the Scheme II.

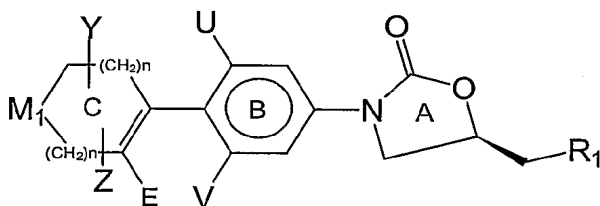
Method B:

The acylation of intermediate amines of Formula V with a heterocyclic acid of Formula VI, such as 2-furoic acid ($Q_1 = O$; $Q_2 = C$; $G, J, L = H$; $R_{12} = \text{COOH}$) gives products of Formula II, wherein $W = \text{CO}$, as shown in the Scheme II wherein U, V, Y, Z, X, W, Q_1 , G, J, L, R_{12} and E are as defined earlier.

Alternatively, the compounds having carbonyl link can also be made by reacting heteroaromatic compound of the Formula VI, such as N-methyl pyrrole with the intermediate amine of Formula V, in the presence of triphosgene or phosgene. The carbonyl linkers may also be introduced between heteroaromatic compound, such as 3-bromothiophene and the amine of Formula V with carbon monoxide in the presence of a catalyst, such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$. The extended chain pyrroles having dicarbonyl linkers can also be obtained from treatment with oxalyl chloride and the amine of the Formula V.

The reduction of the carbonyl linkers using the standard reducing agents results in the formation of methylene linkers.

Mainly amine of Formula V



Formula V

was used for the preparation of compounds of Formula I and Formula II, for example following two specific amines, identified as two different cores, namely

(S)-N-[[3-[3-Fluoro-4-[N-1-(1,2,5,6-tetrahydropyrid-4-yl)]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (**Core I**)

5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one (**Core II**)

were used for the preparation of analogs.

The key intermediate amines of Formula V for the analogue preparation were prepared from commercially available reagents, wherein M_1 is NH, NHR_{13} , $-CH_2NHR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy and R_1 , U, V, Y, Z and E are as defined earlier.

5 Some amines of Formula V are already known in the literature and are given by reference and if they have been made for the first time or by different procedures or variation of known procedure, they are described in detail in the experimental section.

10 The optically pure amines of Formula V could be obtained either by one of a number of asymmetric syntheses or alternatively by resolution from a racemic mixture by selective crystallization of a salt prepared, with an appropriate optically active acid, such as dibenzoyl tartrate or 10-camphorsulfonic acid, followed by treatment with base to afford the optically pure amine.

15 The transformations effected are described in the experimental section. In the above synthetic methods, where specific acids, bases, solvents, catalysts, oxidising agents, reducing agents etc. are mentioned, it is to be understood that the other acids, bases, solvents, catalysts, oxidising agents, reducing agents etc. may be used. Similarly, the reaction temperature and duration of the reaction may be adjusted according to the desired need.

20 Particular compounds which are capable of being produced by the above mentioned schemes include:

Compound No.	Chemical Name
---------------------	----------------------

- | | |
|----------|---|
| 1. | (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl(5-nitro)methyl} 1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, |
| 25
2. | (S)-N-[[3-[3-Fluoro- 4-[N-1-{2-thienyl (5-nitro) methyl}] 1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, |
| 3. | (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide, |

4. 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl] 1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one,
5. 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one.

5 Most of the compounds were characterized using NMR, IR and were purified by chromatography. Crude products were subjected to column chromatographic purification using silica gel (100-200 or 60-120 mesh) as stationary phase.

10 The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation for the particular compounds. The examples are given to illustrate the details of the invention and should not be constrained to limit the scope of the present invention as defined by the claims.

EXAMPLE 1

Analog of (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Core I)

15 (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (core I) was prepared according to procedures described in PCT patent application WO 97/30995 and U.S. Patent No. 6,051,716.

Method A:

General Procedure:

20 The reductive alkylation of the amine intermediate of Formula V with the corresponding heterocyclic aldehydes of the Formula VI, using known reducing agents well known to one of ordinary skill in the art such as sodium triacetoxymethylborohydride or sodium cyanoborohydride gave the products of Formula II wherein $W=CH_2$.

The following compounds were made using this method:

25

Compound No.1: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl(5-nitro)methyl}]1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

To a solution of (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride (0.14 g, 0.38 mmol) in tetrahydrofuran (10 mL), 5-nitro-2-furaldehyde (0.081 g, 0.57 mmol) and molecular sieves added and stirred at RT for 30 min. Then, sodium triacetoxyborohydride (0.32 g, 1.53 mmol) was added and further stirred for 17hrs. The reaction mixture was filtered and the filtrate evaporated in vacuo. The residue obtained was dissolved in dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was purified by column chromatography, eluting with 2% MeOH/dichloromethane.

¹H NMR(CDCl₃) δppm: 7.4 (d, 1H, Ar-H), 7.1-7.3 (3H, Ar-H), 6.4 (d, 1H, Ar-H), 6.1 (t, 1H, NH), 6.0 (s, 1H, double bond H), 4.7 (m, 1H, CH), 4.1 (t, H, CH), 3.4-3.8 (m, 5H), 3.4 (m, 2H, CH₂), 2.8 (m, 2H, 4.1 (t, H, CH), 3.4-3.8 (m, 5H), 3.4 (m, 2H, CH₂), 2.8 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 2.0 (s, 3H, CH₃).

Compound No 2: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl(5-nitro)methyl}]1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The title compound was prepared using (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride and 5-nitro-2-thiophenecarboxaldehyde according to Method A, Compound No. 1.

¹H NMR (CDCl₃) δppm: 6.0-7.8 (m, 5H, Ar-H) 6.0 (m, 2H (NH and double bond H) 4.79 (m, 1H, CH), 4.18 (t, 2H, CH₂) 3.6-3.8 (m, 5H), 3.2 (m, 2H, CH₂) 2.7 (m, 2H, CH₂), 2.4 (m, 2H CH₂), 2.0 (s, 3H, CH₃).

Method B

General Procedure:

For the preparation of compound of Formula I wherein W is equal to C = O, the corresponding acid of Formula VI is used and the amine of Formula V is acylated through

activated esters in the presence of condensing agents such as 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), along with 1-hydroxybenzotriazole. Other methods of acylation can also be employed.

5 The following compounds were prepared using this method:

Compound No 3: (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}]-1,2,5,6-tetrahydropyrid-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide.

To a solution of (S)-N-[[3-[3-Fluoro-4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride (0.18 g, 0.49 mmol) in N,N-dimethyl
10 formamide which was cooled to 0°C, N-methylmorpholine (0.16g, 1.57 mmol), and 1-hydroxybenzotriazole (0.065g, 0.49 mmol) were added and stirred for 30 min. Then, 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was added and the reaction mixture was stirred at room temperature for 17hrs. The reaction mixture was evaporated in vacuo and the residue was taken in dichloromethane. The organic layer was
15 washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The crude product was purified by column chromatography, eluting with 2% MeOH/dichloromethane.

¹HNMR(CDCl₃) δppm: 7.8 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H) 7.2 (m, 3H, Ar-H), 6.0 (t, 1H, NH), 6.0 (broad, s, 1H, double bond H), 4.7 (m, 1H, CH), 3.7-4.5 (m, 8H, CH₂), 2.6 (m,
20 2H, CH₂) 2.6 (m, 2H, CH₂), 2.0 (s, 3H, CH₃)

IR: 1704, 1605 cm⁻¹

EXAMPLE 2

Analogs of 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one (Core II)

25 The amine, 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one was prepared according to the procedure described in PCT patent application WO 00/21960.

Compound No.4: 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one

To a solution of 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[4-(1,2,5,6-tetrahydropyrid-4-yl)phenyl]oxazolidin-2-one hydrochloride (0.43 gm, 0.905 mmole) in tetrahydrofuran (10 ml), was added 5-nitro-furan-2-carboxaldehyde (0.191 gm, 1.35 mmole) and molecular seive (0.4 gm) at room temperature. The reaction mixture was stirred for half an hour. It was followed by the addition of sodium triacetoxo borohydride (0.575 gm, 2.715 mmole) and further stirred for 3hrs. The reaction mixture was filtered, washed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated solution of sodium bicarbonate, followed by washing with brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product obtained was purified by column chromatography, eluting with 1% methanol in dichloromethane.

Yield = 0.4gm.

¹HNMR (CDCl₃) δppm: 8.25 (d, 1H), 7.38 (d, 1H), 7.21-7.15 (m, 2H), 6.54 (d, 2H), 5.95 (m, 1H), 6.07 (m, 1H), 4.71 (d, 1H), 4.35-4.33 (t, 1H), 4.14-4.06 (m, 2H), 3.82-3.78 (m, 2H), 3.27-3.26 (m, 2H), 2.82-2.78 (m, 2H), 2.57 (m, 2H), 1.55 (s, 9H)

Compound No. 5: 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl) methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one

To a solution of 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one (0.4 g, 0.69 mmol) in dichloromethane at 0 °C, trifluoroacetic acid was added and the reaction mixture was stirred at room temperature for 3 hrs. The reaction mixture was evaporated in vacuo. The residue was taken in ethyl acetate and neutralized with ammonium hydroxide, and washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated in vacuo. The crude product was purified by column chromatography, eluting with 1% MeOH in dichloromethane to yield 0.16 g of the title product.

¹H NMR (CDCl₃) δppm: 8.06 (d, 1H), 7.41-7.16 (m, 4H), 6.54 (d, 1H), 5.95 (m, 1H), 5.87 (m, 1H), 4.95 (m, 1H), 4.72 (d, 1H), 4.39 (m, 1H), 4.08 (t, 1H), 3.87-3.71 (m, 3H), 3.63-3.61 (m, 1H), 3.27-3.26 (m, 2H), 2.82-2.78 (m, 2H), 2.56 (m, 2H).

EXAMPLE 3

5 Pharmacological Testing

The compounds of the invention display antibacterial activity when tested by the agar incorporation method. The following minimum inhibitory concentrations (μg/ml) were obtained for representative compounds of the invention which are given below in the following Table 1.

10 GUIDE TO TABLE ABBREVIATIONS:

- 1) *S.aureus* ATCC 25923 --*Staphylococcus aureus* ATCC 25923
- 2) MRSA 15187 --Methicillin Resistant *Staphylococcus aureus*
- 3) *Ent. faecalis* ATCC 29212 --*Enterococcus faecalis* ATCC 29212
- 4) *Ent. faecium* 6A -- *Enterococcus faecium* 6A Van[®], Cipro[®]
- 15 5) *Strep. pne.* ATCC 6303 --*Streptococcus pneumoniae* ATCC 6303
- 6) *Strep.pyog.* ATCC 19615 --*Streptococcus pyogenes*
- 7) *S. epidermidis* - *Staphylococcus epidermidis* ATCC 12228

TABLE - 1

In vitro minimum inhibitory concentrations ($\mu\text{g/ml}$)

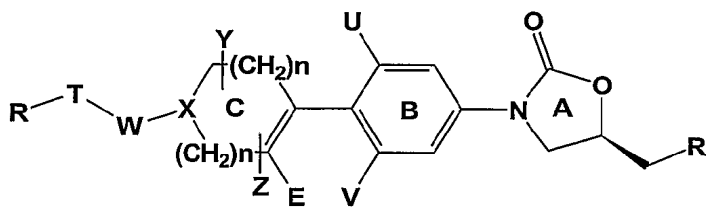
Compound No.	S.aureus 25923	MRSA 15187	MRSA 562	MRSA 33	E. faecalis	VRE	S.pyogenes 19615	S.pneum 6303	S.pneum AB 34
1.	1	0.5	0.5	1	1	1	<0.125	0.5	0.5
3.	<0.125	<0.125	<0.125	<0.125	0.25	0.25	<0.125	0.25	0.5
2.	2	2	1	1	2	2	0.125	0.5	1
5.	1	1	1	1	1	1	1	1	1
Linezolid	2	1	2	2	2	2	2	2	4
Vancomycin	1	0.5	0.5	0.5	4	>16	0.5	0.5	0.25

The in vitro antibacterial activities of the compounds were demonstrated by the agar incorporation method (NCCLS M 7 and M 100-S8 documents). Briefly, the compounds were dissolved in dimethylsulfoxide and doubling dilution of the compounds were incorporated into Meer Hilton agar before solidification. Inoculum was prepared by suspending 4 to 5 colonies into 5 ml of normal saline solution and adjusting the turbidity to 0.5 Macfarland turbidity standard tables (1.5×10^8 CFU/ml), after appropriate dilutions, 10^4 CFU/spot was transferred into the surface of dried plate and incubated for 18 hours (24 hours for MRSN studies). The concentration showing no growth of the inoculated culture was recorded as the MIC. Appropriate ATCC standard strains were simultaneously tested and the result recorded only when the MIC's against standard antibiotics were within the acceptable range.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. Compounds having the structure of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, polymorphs, enantiomers, diastereomers, N-oxides, prodrugs or metabolites, wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring C with a linker W, and further substituted by a group represented by R, wherein R is H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅, N(R₆, R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆, R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH=N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with one or more F, Cl, Br, I, OR₄, SR₄, wherein R₄ is hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxycarbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH; R₅ is H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br and I, OR₅, SR₄, N(R₆, R₇); R₁₀= H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3;

X is CH, CH-S, CH-O, N or CHNR₁₁, wherein R₁₁ is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1 - C_4);

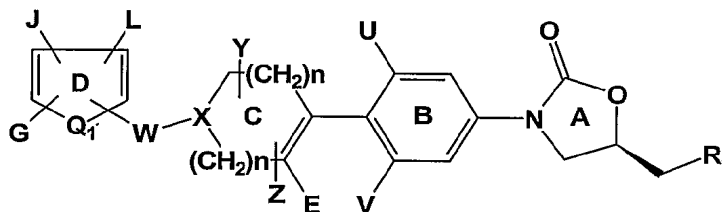
Y and **Z** are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and **V** are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is $(CH_2)_{0-n'}$, CO, CH_2NH , $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, S, $CH_2(CO)$, NH, O, NR_{11} , $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2 , SO, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R₁ is $-NHC(=O)R_2$, $N(R_3, R_4)$, OR_3 , $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxy carbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

2. Compounds having the structure of Formula II:



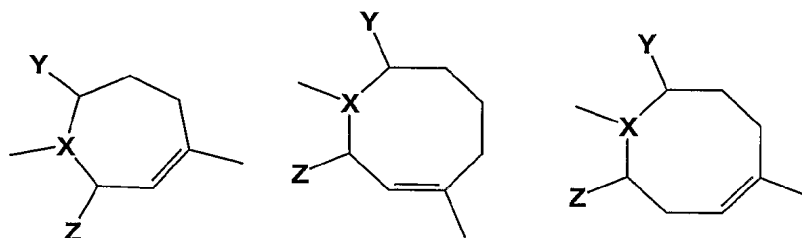
Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

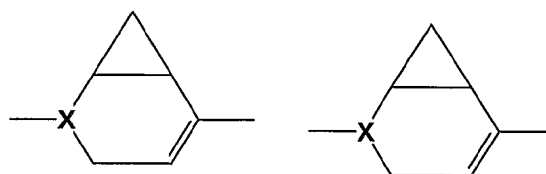
R₁ is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2 , R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy,

- 11 aryl, heteroaryl, C₁₋₆ alkoxy carbonyl or C₁₋₆ alkyl substituted with one or more of
12 F, Cl, Br, I or OH;
- 13 U and V are independently hydrogen, optionally substituted C₁₋₆ alkyl, F, Cl, Br,
14 C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I;
- 15 Y and Z are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl, C₀₋₃ bridging
16 group;
- 17 X is CH, CH-S, CH-O, N or CHNR₁₁, wherein R₁₁ is hydrogen, optionally
18 substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl carbonyl, C₁₋₆
19 alkylcarboxy, aryl or heteroaryl;
- 20 E is hydrogen, hydroxy or lower alkyl (C₁₋₄);
- 21 W is (CH₂)_{0-n'}, C=O, CH₂NH, NHCH₂, CH₂NHCH₂, CH₂N(R₁₁)CH₂, CH₂N(R₁₁),
22 CH(R₁₁), S, CH₂(C=O), NH, O, (CO)CH₂, N(R₁₁)CON(R₁₁), SO₂, SO, NR₁₁,
23 N(R₁₁)C(=S)N(R₁₁), wherein n' is an integer in the range from 0 to 3; R₁₁ is
24 hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆
25 alkyl carbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl;
- 26 Q₁ is O, S or NR₁₁, wherein R₁₁ is as defined above;
- 27 G, J, L are independently H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅,
28 N(R₆, R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆, R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH
29 = N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with
30 one or more of F, Cl, Br and I, OR₄, SR₄, wherein R₄ is as defined above; R₅ is H,
31 C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of
32 F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently H, optionally
33 substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently
34 H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I,
35 OR₅, SR₄, N(R₆, R₇); R₁₀ = H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆
36 alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and
- 37 n is an integer in the range from 0 to 3.

- 1 3. A compound according to claim 2, wherein in Formula II, ring C is 6-8 membered
 2 in size and the ring may have either two or three carbon atoms between each
 3 nitrogen atom, comprising:

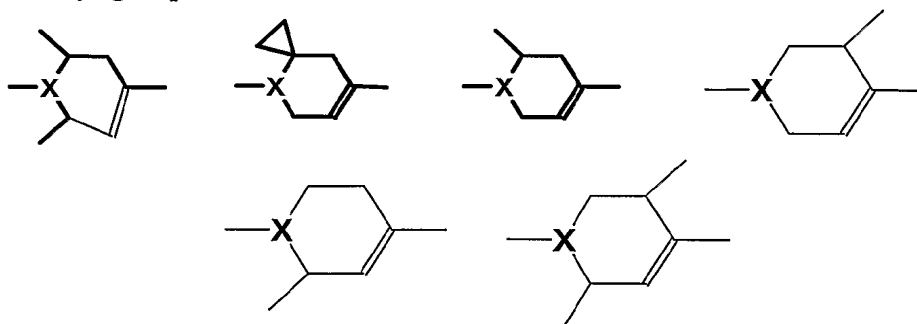


7 and the ring C may be bridged to form a bicyclic system as shown below:



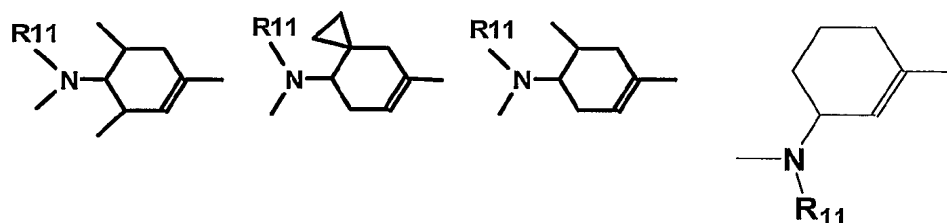
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- 1 4. A compound according to claim 2, wherein in Formula II, ring C is substituted
 2 at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group,
 3 carboxylic and corresponding esters, amides, substituted alkyls or bridging
 4 alkyl groups as shown below:

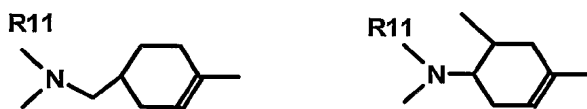


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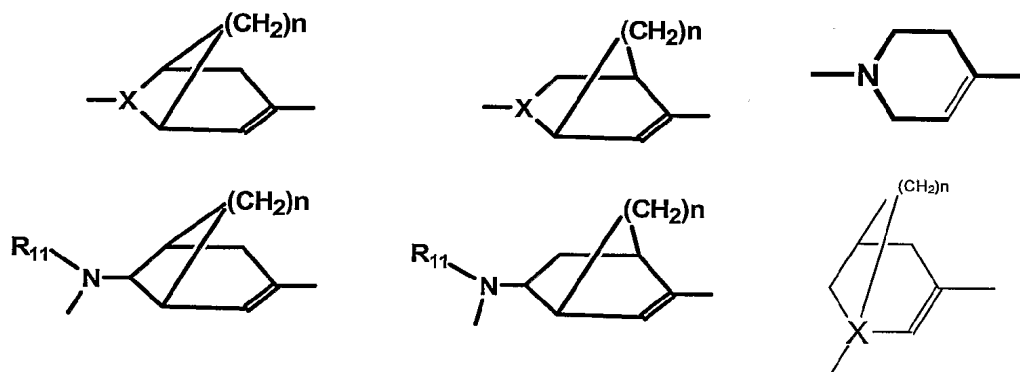
- 1 5. A compound according to claim 2, wherein in Formula II, ring C is 6-
 2 membered in size and X is -CH-(NHR₁₁), or -CHCH₂NHR-, the ring C is
 3 selected from the group consisting of the following rings wherein R₁₁ is as
 4 defined earlier,



6

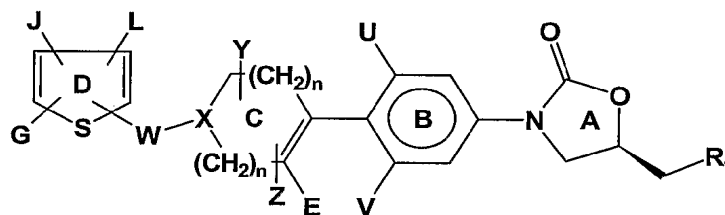


or in addition to the above, the ring C also includes the following structures:



wherein n is as defined earlier.

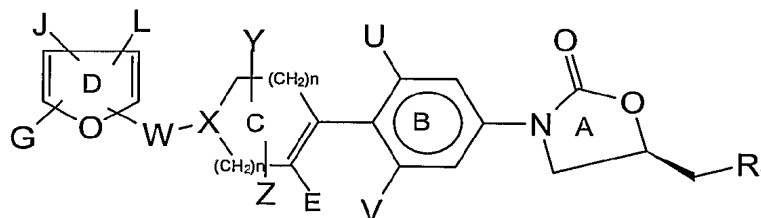
6. A compound according to claim 2 having the structure of Formula III,



Formula III

wherein R, U, V, Y, Z, E, X, W, G, J, L and n are as defined earlier.

7. A compound according to claim 2 having the structure of Formula IV,



Formula IV

wherein R₁, U, V, X, Y, Z, E, W, G, J, L and n are as defined earlier.

1 8. A compound selected from the group consisting of:

2 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl(5-nitro)methyl} 1,2,5,6-tetrahydropyrid-4-yl]
3 phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound No. 1)

4 (S)-N-[[3-[3-Fluoro- 4-[N-1-{2-thienyl (5-nitro) methyl}] 1,2,5,6-tetrahydropyrid-
5 4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound No. 2)

6 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienoyl(5-nitro)}-1,2,5,6-tetrahydropyrid-4-
7 yl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (Compound No. 3)

8 5(S)-Isoxazol-3-yl-amino-(N-t-butoxycarbonyl)-N-methyl-3-[3-Fluoro-4-[N-1-(5-
9 nitro-2-furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one
10 (Compound No. 4)

11 5(S)-Isoxazol-3-yl-aminomethyl-3-[3-Fluoro-4-[N-1-(5-nitro-2-
12 furyl)methyl]1,2,5,6-tetrahydropyrid-4-yl]phenyl]oxazolidin-2-one (Compound
13 No. 5).

1 9. A pharmaceutical composition comprising a compound of claims 1, 2, or 8 and a
2 pharmaceutical acceptable carrier.

1 10. A pharmaceutical compositon comprising a pharmaceutically effective amount of a
2 compound according to claims 1, 2 or 8 or a physiologically acceptable acid
3 addition salt thereof with a pharmaceutically acceptable carrier for treating
4 microbial infections.

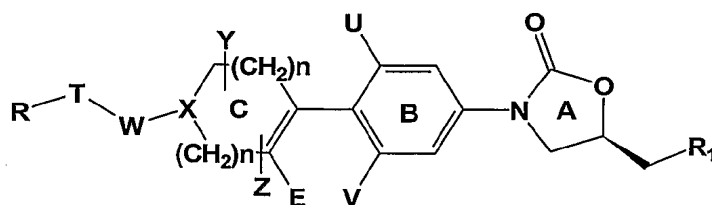
1 11. A method of treating or preventing microbial infections in a mammal comprising
2 administering to said mammal, the pharmaceutical composition according to claim
3 9.

1 12. The method according to claim 11, wherein the microbial infections are caused by
2 gram-positive and gram-negative bacteria.

1 13. The method according to claim 12, wherein the gram-positive bacteria are selected
2 from the group consisting of staphylococcus spp., streptococcus spp., enterococci

spp., bacillus spp., corynebacterium spp., clostridia spp., peptostreptococcus spp.,
listeria spp. and legionella spp.

14. A method of treating or preventing aerobic and anaerobic bacterial infections in a mammal comprising administering to said mammal, a therapeutically effective amount of a compound having the structure of Formula I



Formula I

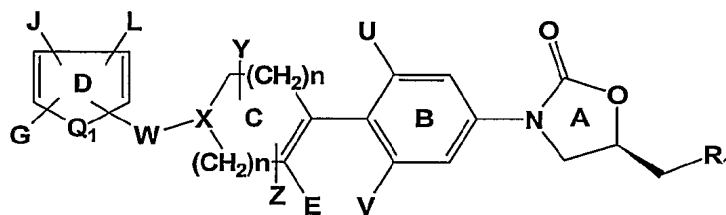
and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring C with a linker W, and are further substituted by a group represented by R, wherein R is H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅, N(R₆,R₇), NHCOC(R₈, R₉, R₁₀), CON(R₆,R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉, -CH=N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I, OR₄, SR₄, wherein R₄ is hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxycarbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH; R₅ is H, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br and I, OR₅, SR₄, N(R₆,R₇); R₁₀= H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and

n is an integer in the range from 0 to 3;

- 26 **X** is CH, CH-S, CH-O, N or CHNR₁₁, wherein R₁₁ is hydrogen, optionally
 27 substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl,
 28 C₁₋₆ alkylcarboxy, aryl or heteroaryl;
 29 **E** is hydrogen, hydroxy or lower alkyl (C₁₋₄);
 30 **Y** and **Z** are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl or C₀₋₃ bridging
 31 groups;
 32 **U** and **V** are independently hydrogen, optionally substituted C₁₋₆ alkyl, F, Cl, Br, I,
 33 C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I;
 34 **W** is (CH₂)_{0-n'}, CO, CH₂NH, -NHCH₂, -CH₂NHCH₂, -CH₂-N(R₁₁)CH₂-,
 35 CH₂(R₁₁)N-, CH(R₁₁), S, CH₂(CO), NH, O, NR₁₁, (CO)CH₂, N(R₁₁)CON(R₁₁),
 36 N(R₁₁)C(=S)N(R₁₁), SO₂, SO, wherein n' is an integer in the range from 0 to 3; R₁₁
 37 is hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆
 38 alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl; and
 39 **R₁** is -NHC(=O)R₂, N(R₃, R₄), OR₃, -NR₂C(=S)R₃, -NR₂C(=S)SR₃, wherein R₂ is
 40 hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one
 41 or more of F, Cl, Br, I, OH; R₃, R₄ are independently hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂
 42 cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxycarbonyl or C₁₋₆ alkyl
 43 substituted with one or more of F, Cl, Br, I or OH.

- 1 15. A method of treating or preventing aerobic and anaerobic bacterial infections in
 2 mammal comprising administering to said mammal, a therapeutically effective
 3 amount of a compound having the structure of Formula II



7 Formula II

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R_1 is $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ or $-OR_3$, wherein R_2 , R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxy carbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH;

U and V are independently hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and Z are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is CH, CH-S, CH-O, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1 - C_4);

W is $(CH_2)_{0-n'}$, C=O, CH_2NH , $NHCH_2$, CH_2NHCH_2 , $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, S, $CH_2(C=O)$, NH, O, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2 , SO, NR_{11} , $N(R_{11})C(=S)N(R_{11})$, wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl carbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

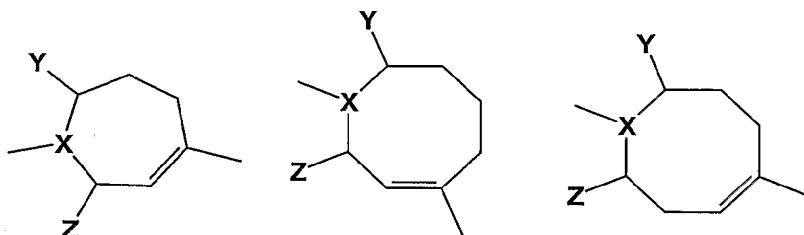
Q_1 is O, S or NR_{11} , wherein R_{11} is as defined above;

G, J, L are independently H, C_{1-6} alkyl, F, Cl, Br, I, $-CN$, COR_5 , $COOR_5$, $N(R_6, R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2 , NO_2 , CH_2R_8 , CHR_9 , $-CH=N-OR_{10}$, $-C=CH-R_5$, OR_5 , SR_5 , $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_4 , SR_4 , wherein R_4 is as defined above; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently

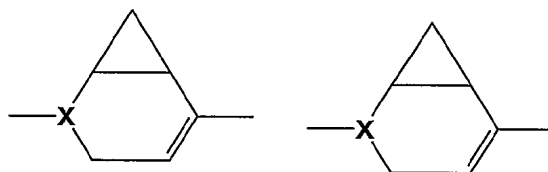
36 H, C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I,
 37 OR₅, SR₄, N(R₆,R₇); R₁₀= H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl,
 38 C₁₋₆ alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and

39 n is an integer in the range from 0 to 3.

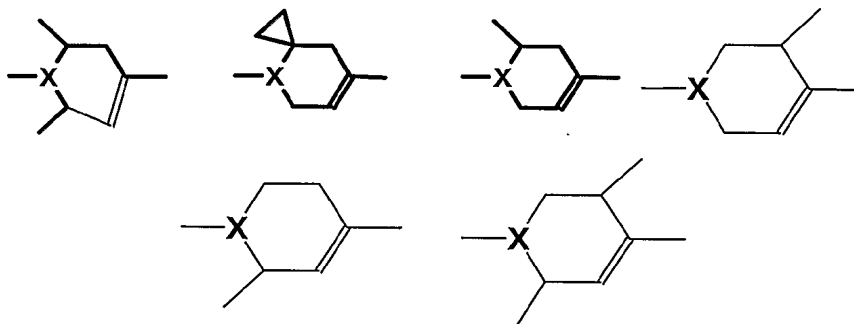
1 16. The method according to claim 15 wherein in Formula II, the ring C is 6-8
 2 membered in size and the ring may have either two or three carbon atoms between
 3 each nitrogen atom, comprising



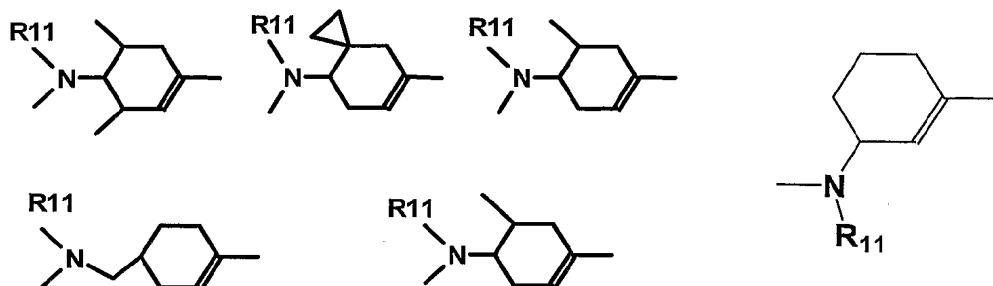
8 and the ring C may be bridged to form a bicyclic system as shown below:



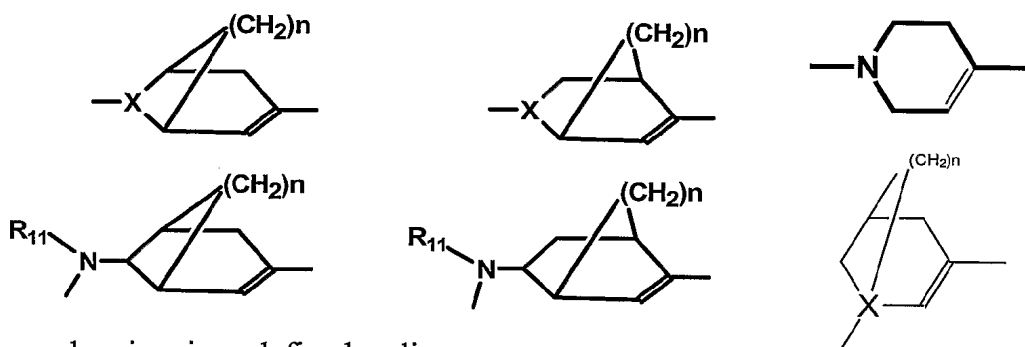
1 17. The method according to claim 15, wherein in Formula II, the ring C is substituted
 2 at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic
 3 and corresponding esters, amides, substituted alkyls or bridging alkyl groups as
 4 shown below:



18. The method according to claim 15, wherein in Formula II, the ring C is 6-membered in size and X is -CH-(NHR), or -CHCH₂NHR-, the ring C is selected from the group consisting of the following rings wherein R₁₁ is as defined earlier,

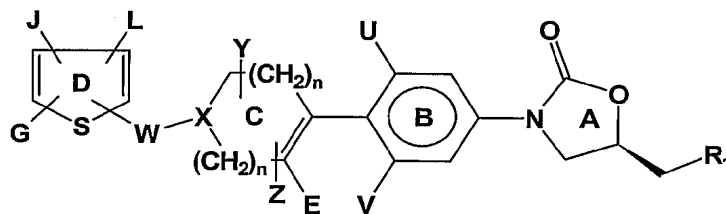


or in addition to the above, the ring C also includes the following structures:



wherein n is as defined earlier.

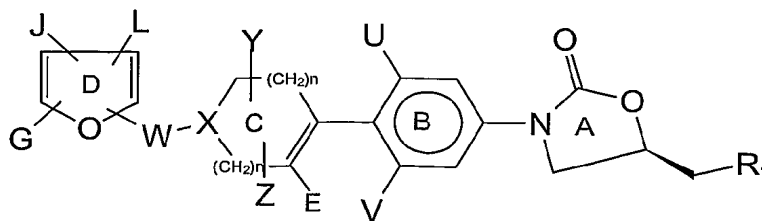
19. The method according to claim 15 having the structure of Formula III,



Formula III

wherein R₁, U, V, E, Y, Z, X, W, G, J, L and n are as defined earlier.

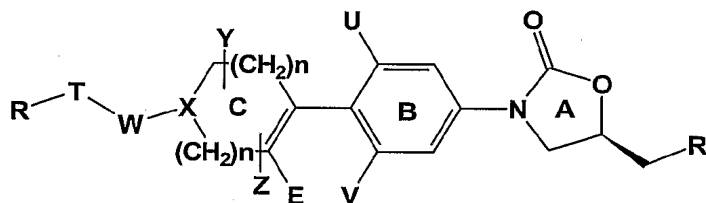
20. The method according to claim 15 having the structure of Formula IV



Formula IV

wherein R_1 , U, V, X, Y, Z, W, G, J, L, E and n are as defined earlier.

21. A process for preparing compounds of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

T is a five to seven membered heterocyclic ring, substituted heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker **W**, and further substituted by a group represented by **R**, wherein **R** is H, C_{1-6} alkyl, F, Cl, Br, I, $-CN$, COR_5 , $COOR_5$, $N(R_6, R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2 , NO_2 , CH_2R_8 , CHR_9 , $-CH=N-OR_{10}$, $-C=CH-R_5$, OR_5 , SR_5 , $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4 , SR_4 , wherein R_4 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxycarbonyl or C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; R_5 is H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more F, Cl, Br, I or OH, aryl or heteroaryl; R_6 and R_7 are independently H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br and I, OR_5 , SR_4 ,

$N(R_6, R_7)$; $R_{10} = H$, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is CH , $CH-S$, $CH-O$, N or $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl;

E is hydrogen, hydroxy or lower alkyl (C_1-C_4);

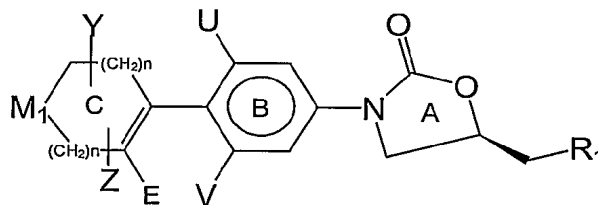
Y and Z are independently hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging groups;

U and V are independently hydrogen, optionally substituted C_{1-6} alkyl, F , Cl , Br , I , C_{1-12} alkyl substituted with one or more of F , Cl , Br , I ;

W is $(CH_2)_{0-n'}$, CO , CH_2NH , $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, S , $CH_2(CO)$, NH , O , NR_{11} , $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2 , SO , wherein n' is an integer in the range from 0 to 3; R_{11} is hydrogen, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarboxy, aryl or heteroaryl; and

R_1 is $-NHC(=O)R_2$, $N(R_3, R_4)$, OR_3 , $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F , Cl , Br , I , OH ; R_3 , R_4 are independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, aryl, heteroaryl, C_{1-6} alkoxy carbonyl or C_{1-6} alkyl substituted with one or more of F , Cl , Br , I or OH ;

comprising reacting an amine compound of Formula V



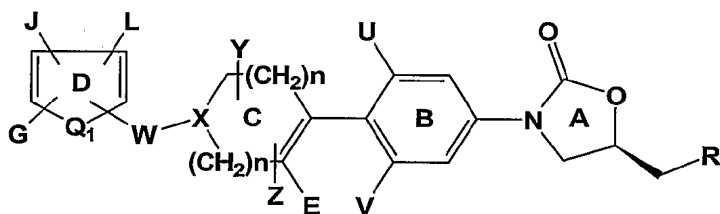
Formula V

with a heteroaromatic compound of Formula R-T-W-R₁₂, wherein M₁ is selected from the group consisting of NH, NHR₁₃, -CH₂NR₁₃, wherein R₁₃ is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy and R, T, W, R₁, U, V, Y, Z and E are as defined earlier and R₁₂ is a suitable leaving group selected from the group consisting of fluoro, chloro, bromo, SCH₃, -SO₂CH₃, -SO₂CF₃, Tos, OC₆H₅, -COOH or -CHO.

22. The process according to claim 21 for preparing compounds of Formula I, wherein W=CH₂ and R-T-W-R₁₂ is a heteroaromatic compound with an aldehyde group and the compound of Formula I is produced by reductive amination.

23. The process according to claim 21 for preparing compounds of Formula I, wherein W=CO and the amine compound of Formula V is acylated with activated esters in the presence of condensing agents selected from the group consisting of 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC).

24. A process for preparing compounds of Formula II



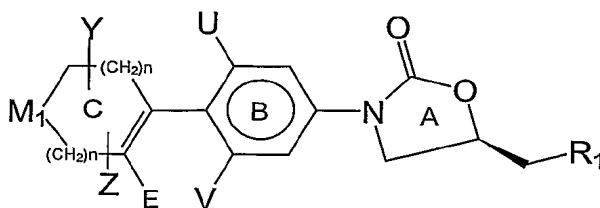
Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

R₁ is -NHC(=O)R₂, -N(R₃,R₄), -NR₂C(=S)R₃, -NR₂C(=S)SR₃ or -OR₃, wherein R₂, R₃, R₄ are independently hydrogen, C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, aryl, heteroaryl, C₁₋₆ alkoxy carbonyl or C₁₋₆ alkyl substituted with one or more of F, Cl, Br, I or OH;

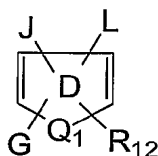
- 12 U and V are independently hydrogen, optionally substituted C₁₋₆ alkyl, F, Cl, Br,
13 C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I;
- 14 Y and Z are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₂ cycloalkyl, C₀₋₃ bridging
15 group;
- 16 X is CH, CH-S, CH-O, N or CHNR₁₁, wherein R₁₁ is hydrogen, optionally
17 substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl carbonyl, C₁₋₆
18 alkylcarboxy, aryl or heteroaryl;
- 19 E is hydrogen, hydroxy or lower alkyl (C₁₋₄);
- 20 W is (CH₂)_{0-n'}, C=O, CH₂NH, NHCH₂, CH₂NHCH₂, CH₂N(R₁₁)CH₂, CH₂N(R₁₁),
21 CH(R₁₁), S, CH₂(C=O), NH, O, (CO)CH₂, N(R₁₁)CON(R₁₁), SO₂, SO, NR₁₁,
22 N(R₁₁)C(=S)N(R₁₁), wherein n' is an integer in the range from 0 to 3; R₁₁ is
23 hydrogen, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl
24 carbonyl, C₁₋₆ alkylcarboxy, aryl or heteroaryl;
- 25 Q₁ is O, S or NR₁₁, wherein R₁₁ is as defined above;
- 26 G, J, L are independently H, C₁₋₆ alkyl, F, Cl, Br, I, -CN, COR₅, COOR₅,
27 N(R₆,R₇), NHCOC(R₈,R₉,R₁₀), CON(R₆,R₇), CH₂NO₂, NO₂, CH₂R₈, CHR₉,
28 -CH=N-OR₁₀, -C=CH-R₅, OR₅, SR₅, -C(R₉)=C(R₉)NO₂, C₁₋₁₂ alkyl substituted with
29 one or more of F, Cl, Br and I, OR₄, SR₄; wherein R₄ is the same as above; R₅ is H,
30 C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl substituted with one or more of
31 F, Cl, Br, I or OH, aryl or heteroaryl; R₆ and R₇ are independently H, optionally
32 substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆ alkoxy; R₈ and R₉ are independently H,
33 C₁₋₆ alkyl, F, Cl, Br, I, C₁₋₁₂ alkyl substituted with one or more of F, Cl, Br, I, OR₅,
34 SR₄, N(R₆,R₇); R₁₀= H, optionally substituted C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₁₋₆
35 alkoxy, C₁₋₆ alkyl, aryl or heteroaryl; and
- 36 n is an integer in the range from 0 to 3;

comprising reacting a compound of Formula V



Formula V

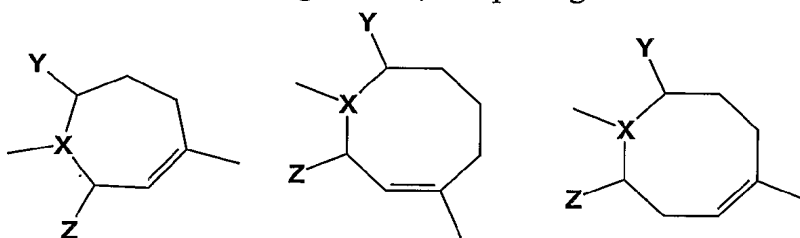
with a heteroaromatic compound of Formula VI



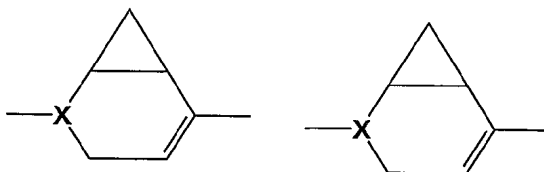
Formula VI

wherein M_1 is NH, NHR_{13} , $-CH_2NR_{13}$, wherein R_{13} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, alkoxy and R, T, W, R_1 , U, V, Y, Z, G, J, L, n, Q_1 and E are as defined earlier and R_{12} is a suitable leaving group selected from the group consisting of fluoro, chloro, bromo, SCH_3 , $-SO_2CH_3$, $-SO_2CF_3$, Tos, OC_6H_5 , $-COOH$ or $-CHO$.

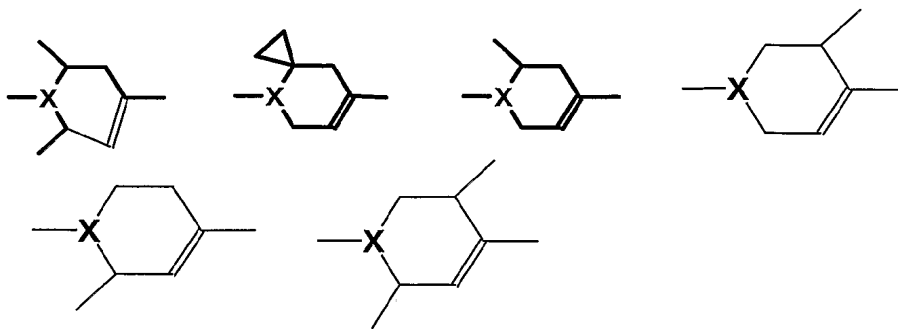
25. The process according to claim 24 for preparing compounds of Formula II, wherein ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, comprising:



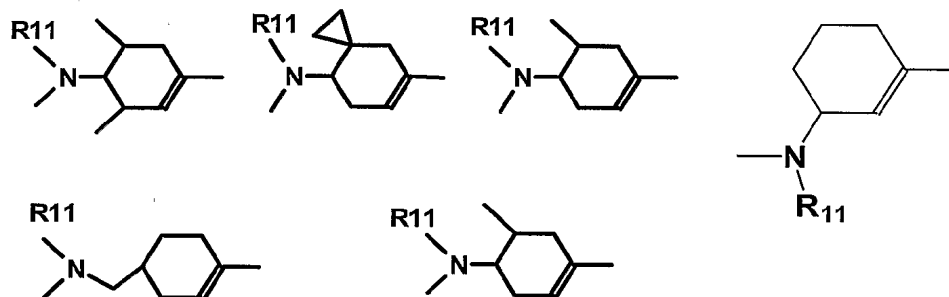
and the ring C may be bridged to form a bicyclic system as shown below:



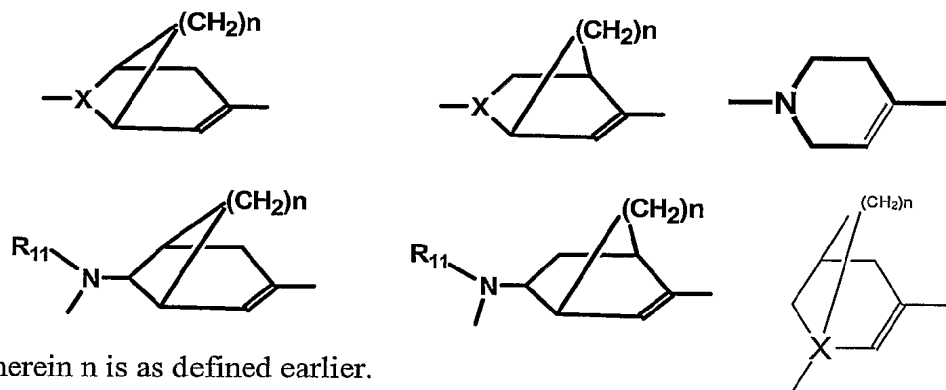
26. The process according to claim 24 for preparing compounds of Formula II, wherein ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups as shown below:



27. The process according to claim 24 for preparing compounds of Formula II, wherein ring C is 6-membered in size and X is -CH-(NHR), or -CHCH₂NHR-, the ring C is selected from the group consisting of the following rings wherein R₁₁ is as defined earlier;

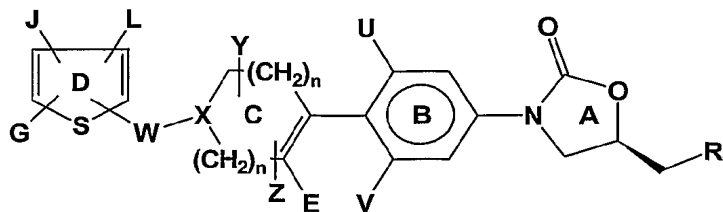


or in addition to the above, the ring C also includes the following structures:



wherein n is as defined earlier.

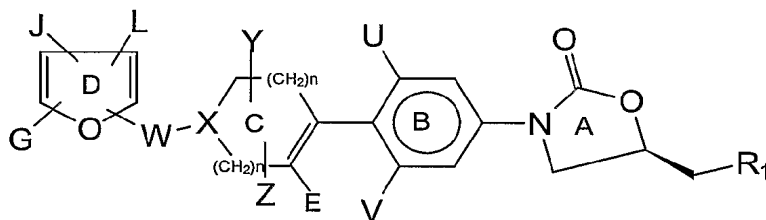
28. The process according to claim 24 having the structure of Formula III



Formula III

wherein R_1 , U, V, Y, Z, E, X, W, G, J, L and n are as defined earlier.

29. The process according to claim 24 having the structure of Formula IV



Formula IV

wherein R_1 , U, V, X, Y, Z, W, G, J, L, E and n are as defined earlier.

30. The process of claim 24, wherein the amine of Formula V reacts with a heteroaromatic compound of Formula VI in a solvent selected from the group consisting of dimethylformamide, dimethylacetamide, ethanol and ethylene glycol.

31. The process of claim 24, wherein the reaction of amine of Formula V with a heteroaromatic compound of Formula VI is carried out in the presence of a base selected from the group consisting of triethylamine, diisopropylamine, potassium carbonate and sodium bicarbonate.

32. The process of claim 24, wherein the reaction is carried out at a temperature ranging from about -70°C to about 180°C .

- 1 33. The process of claim 24, wherein the heteroaromatic compound of Formula VI is
2 furaldehyde.
- 1 34. The process of claim 24, wherein the heteroaromatic compound of Formula VI is
2 2- furoic acid.

INTERNATIONAL SEARCH REPORT

Internat application No

PCT/IB 03/01754

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 A61K31/422 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003 027083 A (MERCK & CO., INC., USA; KYORIN PHARMACEUTICAL CO., LTD.) 3 April 2003 (2003-04-03) claim 6; example 134 ---	1,9-14, 21-23
X	WO 99 64417 A (ZENECA LIMITED, UK) 16 December 1999 (1999-12-16) Claims and compounds of ex. 3, 11, 13, 15, 17, 26, 28, 31, 32, 34, 59, 131, 133, 137 and 167. ---	1,9-14, 21-23
X	WO 97 30995 A (ZENECA LTD., UK; GRAVESTOCK, MICHAEL BARRY) 28 August 1997 (1997-08-28) cited in the application claims, compounds of examples 12-13, 25-26, 37-38 and several compounds of table A p. 79 and table B p.81-82 --- -/--	1,2,6, 9-15,19, 21-24, 28,30-32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

25 November 2003

Date of mailing of the international search report

21/01/2004

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Authorized officer

Gregoire, A

INTERNATIONAL SEARCH REPORT

Internati Application No

PCT/1B 03/01754

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2000 021960 A (ZENECA LIMITED, UK) 20 April 2000 (2000-04-20) cited in the application claim 6; example 47 ---	1,9-14, 21-23
X	WO 99 10342 A (ZENECA LIMITED, UK) 4 March 1999 (1999-03-04) claims 1,2 ---	1,9-14, 21-23
X	WO 97 09328 A (UPJOHN CO., USA; HUTCHINSON, DOUGLAS, K.; ENNIS, MICHAEL D.; HOFFMAN, R) 13 March 1997 (1997-03-13) claims 1,2 ---	1,9-14, 21-23
X	WO 2003 072575 A (ASTRAZENECA AB, SWED.; ASTRAZENECA UK LIMITED) 4 September 2003 (2003-09-04) Intermediates 54 and 57 on pages 107 and 111 ---	1,21-23
X	WO 2002 096916 A (ASTRAZENECA AB, SWED.; ASTRAZENECA UK LIMITED) 5 December 2002 (2002-12-05) Intermediates of steps 4 and 5 page 10 -----	1,21-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/01754

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-7(part), 9-34(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7(part), 9-34(part)

Claims 1-7 and 9-34, in as far as the expressions "prodrugs" and "metabolites" are explicitly or implicitly concerned, is so unclear (Article 6 PCT) that a meaningful international search is impossible with regard to these expressions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/IB 03/01754

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Internati pplication No

PCT/IB 03/01754

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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